REMARKS

Claims 1-18 are presently pending in this Application. In the instant Amendment, Applicants have canceled Claims 17-18, without prejudice, have amended Claims 1-16, and have added new Claims 19-20. Support for amended Claims 1-16 as well as new Claims 19-20 can be found generally throughout the instant Specification, and in and Claims 1-18 as filed. Attached hereto is a marked-up version of the changes made to the amended Claim by the instant Amendment. The attached page is captioned "**Version With Markings To Show Changes Made.**"

The Drawings

The Examiner has asserted that formal drawings must be filed. In response, Applicants file herewith eight (8) sheets of formal drawings for the instant Application.

The Specification

The Examiner has required the submission of a substitute Specification that uses proper idiomatic English and complies 37 CFR 1.52(a) and (b). The Examiner has also required the substitute Specification be accompanied with a statement that it contains no new matter. In response to this requirement, filed herewith is (1) a substitute Specification that uses proper idiomatic English; (2) an interlineated copy of the substitute specification showing changes made with respect to the instant Specification as filed; and (3) Statement under 37 CFR 1.125 that the substitute Specification contains no new matter; and (4) transmittal form for substitute Specification.

The Pending Claims Are In Proper Form

The Examiner has objected to Claim 16 under 37 CFR 1.75(c) as being in improper form

because a multiple dependent Claim can not depend from another multiple dependent Claim. In of the Examiner's position, the Examiner has not further treated Claim 16 on its merits.

In response, the Claims as amended above possess no multiple dependent Claim that depends upon another multiple dependent Claim. Thus, this objection should be removed.

The Invention is Novel

Claims 1-6, 8, 10-12, 14, 17 and 18 have been rejected under 35 U.S.C. § 102(a) as being anticipated by the teachings of WO 93/09236 (the '236 application). The Examiner has asserted that the '236 application teaches a myogenic vector system (MVS) that is comprised of a promoter active in skeletal, heart and smooth muscle cells. (p. 9, lines 9-12). It is the Examiner's belief that the promoter of the '236 application can be skeletal α-actin with a variety of other sequences (a 5' mRNA leader sequence, an intron, an ATG initial codon, an NcoI restriction side, 3' untranslated regions (page 10, lines 3-12)). The Examiner has also asserted that in the broadest reading of the instant Invention, the MVS contains part of an enhancer and part of a promoter specific in muscle and even part of Smact or SM22, and such part can mean as little as one nucleotide. Yet, it is the Examiner's opinion that the '236 application also envisions use of a regulator system of which any of a variety of regulators can be used. In particular, the Examiner has asserted that page 10, lines 23-26 of the '236 application teaches two different regulatory sequences are a preferred embodiment, and that within this embodiment, two functional units are linked together, one with a myogenic specific promoter, and the second with a response element corresponding to a receptor (page 11, lines 1-9 of the '236 application). It is the Examiner's position that this preferred embodiment represents or contains parts of an enhancer and part of a promoter specific in muscle, and even part of Smact or Sm22. In addition,

the Examiner believes the MVS of the '236 application includes sequences for a variety of other proteins such as growth factors, that these sequences are all contained in a cassette (page 12, lines 8-18), and the MVSs are modified to enhance uptake by the cell (page 3, lines 26-28).

This rejection is respectfully traversed. As the Examiner has admitted, the '236 application does not teach such hybrid promoter. Rather, in order to make this rejection, the Examiner asserted that "***In the broadest reading*** of the claimed invention, the MVS contains ***parts*** of an enhancer and part of a promoter specific in muscle and even part of SMact or SM22 (emphasis added)." Yet, Amended Claim 1 is directed towards, *inter alia*, a hybrid promoter that comprises a promoter ***and*** an enhancer region. Thus, the Claims as amended are clearly novel with respect to the teachings of the '236 application, and this rejection should be withdrawn.

Furthermore, Claims 1-6, 8, 10-12, 14 and 17-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by the teachings of WO/98/24922 (the '922 application). The Examiner has asserted that the '922 application teaches vectors for stable expression of IGF-1, which includes sequences necessary for expression of a nucleic acid cassette (see abstract). It is also the Examiner's belief that the vector of the '922 application contains 5' flanking regions for regulated expression of IGF-1. Furthermore, the Examiner believes. The Examiner has also asserted that:

(a) muscle cells used for expression in the '922 application include smooth muscle cells (p. 14, line 28-33);

(b) promoters used in the vector of the '922 application include myogenic–specific promoters such as skeletal α-actin and non-specific promoters such as CMS-IE and RSV-LTR;

(c) a promoter may be used by itself or in combination with elements from other promoters as well as enhancers (p. 10, line 23-26); and

(d) the 5' flanking region can include a promoter sequence which may be linked to other 5' UTR sequences (p. 15, lines 10-14).

With respect to the instant Invention, the Examiner believes it envisions two functional units linked together with one myogenic specific promoter, and the second with a response element corresponding to a receptor that drives expression of a therapeutic protein or RNA (p. 17, lines 18-24 of the instant Application). Moreover, with respect to delivery of the vector, the Examiner believes the instant Invention envisions the use of biochemical transfer agents that include PVP (p. 23, lines 6-13 of the instant Specification), and lipids, proteins or carbohydrates (p. 23, line 22-page 24, line 4 of the instant Specification) for the enhancement of uptake of the vector. Finally, the Examiner has asserted that the instant Specification teaches myogenic cell cultures were transfected with the vector of the instant Invention (p. 52, lines 1-8).

This rejection is respectfully traversed. Initially, it is noted that there is no specific teachings in the '229 application regarding a "hybrid promoter," or even a vector that comprises such a promoter. Rather, the '229 application discloses ***vectors*** for expressing ***IGF*** protein, wherein such a vector comprises a promoter "...used by itself or in combination with elements from other promoters, as well as various enhancers, transcript stabilizers or other sequences capable of enhancing function of the vector." (p. 10, lines 33-36 of the '922 application). Moreover, there is no teachings in the '229 application regarding the relative location of an enhancer and a promoter within the vector described therein. Alberts *et al.* (Molecular Biology of the Cell, 3rd 3Ed., Garland Publishing Co., New York (1994)), which typifies the state of

knowledge in the art at the time of the filing of the priority document for the '922 application, explain that:

> It was surprising to many biologists when, in 1979, it was discovered that DNA sequences ***thousands of nucleotide pairs away*** (emphasis added) from a eucaryotic promoter could activate transcription of the promoter. It is now known that such **enhancer** sequences serve as specific binding sites for gene regulatory proteins that activate or *enhance* transcription and that this sort of "action-at-a-distance" is the rule rather than the exception for gene regulatory proteins in eucaryotic cells.

(*Id* at 422).

Yet, in a hybrid promoter of the amended Claims, the enhancer region and the promoter region ***are less than 1000 base pairs apart***. Support for these amended Claims can be found can be found on page 3, lines 2-4 of the substitute Specification filed herewith (as well on page 2, line 36 of the Specification as filed), wherein Applicants explain, "These two regions are genetically linked and sufficiently close to each other to allow the enhancer region to activate the promoter region. ***Preferably, the distance separating the enhancer region and the promoter region is less than 1 kb*** (emphasis added)." Hence, it is respectfully submitted that Claims 1-6, 8, 10-12, 14 and 17-18 as amended are novel, and this rejection should be withdrawn.

Moreover, Claims 1-11, 15, 17 and 18 have been rejected under 35 U.S.C. § 102(e) as being anticipated by the teachings of U.S. Patent 6, 297,220 filed on November 18, 1997 and issued on October 2, 2001 (the '220 patent). The Examiner has asserted that the '220 patent teaches a recombinant adenovirus that comprises a coding sequence under control of an enhancer-promoter, and the preferred enhancer-promoter sequences of the '220 patent are CMV, RSV, smooth muscle α-actin (column 3, lines 14-24). Furthermore, the Examiner is of the

opinion that the coding sequence of the adenovirus of the '220 patent is operatively linked to a transcription termination region (column 3, lines 24-28), and that the adenovirus is typically delivered as a pharmaceutical composition with a physiologically acceptable carrier (column 3, lines 44-48). Furthermore, the Examiner has asserted that in an adenovirus of the '220 patent, a coding sequence can include any gene product, but that some preferred embodiments include growth factors which act as transcription factors, angiogenesis inducers, etc. (column 6, line 17).

Moreover, the Examiner believes that the enhancer-promoter of the '220 patent is described as a composite unit that contains both enhancer and promoter elements, and is operatively linked to at least one gene product (column 6, lines 40-44). Also, the Examiner has asserted that preferred smooth muscle promoters of the '220 patent include endothelin or smooth muscle α-actin, and that Example 1 discloses that the β-gal gene cassette was inserted into AdCMV (column 11).

It is the Examiner's position that a hybrid promoter of the instant Invention can be read onto the teachings of the '220 patent given the criteria that it is part of an enhancer and part of a promoter such that the inclusions of the smooth muscle α-actin promoter in the construct with the adenoviral genome ensure that adenoviral enhancers will be present and create an enhancer-promoter hybrid promoter. Moreover, it is the opinion of the Examiner that given that the enhancer and promoter need to be a part (a single nucleotide) of the sequences of for example CMV and SM22, then the '220 patent can be read to comprise said sequences.

This rejection is respectfully traversed. Initially, it is noted that the '220 patent teaches that the promoter and enhancer need not be very close to each other in a nucleotide sequence. In particular, at column 6, lines 18-39 of the '220 patent it is explained that the promoter is typically

within 100 nucleotide pairs upstream of the transcription start site, and that the enhancer can function when located at variable distances from the transcription side. Indeed, lines 55-59 of column 6 of the '220 patent state that the enhancer can even be downstream of the initiation start site. In contrast, amended Claim 1 is directed towards, *inter alia,* a hybrid promoter comprising, *inter alia*, a promoter and an enhancer in which the enhancer is located within 1 kb from the promoter. As explained above, support for amended Claim 1 can be found on page 3, lines 2-4 of the substitute specification filed herewith. Hence, this rejection should be withdrawn.

Furthermore, Claims 1-15, 17 and 18 have been rejected under 35 U.S.C. § 102(e) as being anticipated by the teachings of US patent 6,074,850 (the '850 patent). The Examiner has asserted that the '850 patent teaches a viral vector system or plasmid into which an E2F-Rb fusion construct is inserted (column 8, lines 54-64), and administration of such a vector which comprises a solution in an acceptable carrier, which is a liposome in the case of plasmid DNA. (column 10, lines 35-64). Furthermore, the Examiner believes that Example II of the 850 patent discloses the construction of a recombinant adenovirus expressing Rb under control of the smooth muscle α-actin promoter (column15 – column 18), wherein the adenovirus contains the E1A enhancer followed by the human smooth muscle α-actin promoter and the E1b/proteinIX poly A signal. It is the Examiner's opinion that the teachings of the '850 patent encompass the instant Invention because, in a broad reading of the pending Claims in this matter, the enhancer and promoter need to be a part of the sequence, such as CMV and SM22.

For reasons discussed above, this rejection is respectfully traversed. The '850 patent is directed towards a an E2F-Rb fusion protein, and discloses a nucleotide sequence that encodes for such a fusion as well as for methods of making such a fusion. Thus, there are no specific

teachings in the '850 patent regarding a hybrid promoter as disclosed in the instant Application. Just as with the references discussed above, the '850 patent is silent with respect to the location of an enhancer and a promoter in a vector described therein for producing the E2F-Rb fusion. For example, in column 5, lines 66-67 through to column 6, lines 1-8 of the '850 patent, it is explained:

> In general, a construct of the invention is provided in an expression vector comprising the following elements linked sequentially at appropriate distances for functional expression: a tissue-specific promoter, an initiation site for transcription, a 3' untranslated region, a 5' mRNA leader sequence, a nucleic acid sequence encoding a polypeptide of the invention, and a polyadenylation signal. Such linkage is termed "operatively linked." Enhancer sequences and other sequences aiding expression and/or secretion can also be included in the expression vector.

Even the passage the Examiner pointed out is devoid of any teaching regarding the relative locations of the enhancer and the promoter. Hence, contrary to the Examiner's assertions, amended Claims 1-15 and 17-18 are clearly novel, and these rejections should be withdrawn.

The Claims are Definite

Claims 1-15, and 17-18 have been rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the Invention. The Examiner has asserted that Claims 1-15, and 17-18 do not begin with "the" or "a". In response, amended Claims 1-16, as well as new Claims 19-10, begin with "the" or "a". Hence, this rejection should be withdrawn.

Furthermore, the Examiner has asserted that the term "strong" recited in Claim 1 is a relative term that renders the Claim indefinite. In particular, the Examiner believes that no single

set of conditions is recognized by the art as being "strong" because the Specification does not provide a standard for ascertaining the requisite degree. Hence, it is the Examiner's position that the metes and bounds of Claim 1 and by dependendency Claims 3 and 4 can not be established.

In response, Applicants respectfully submit the instant Specification makes the definition of "strong" clear and understandable to one of ordinary skill in the art. In particular, on page 1, lines 25-34 of the instant Specification, Applicants clearly state:

> Another approach involves the use of expression signals specific for certain cell types. In this regard, so-called "specific" promoters have been described in the literature, such as pyruvate kinase promoter, the villin promoter, GFAP, the promoter of the fatty acid-binding intestinal protein, the α-actin promoter of smooth muscle cells, the SM22 promoter, or the promoter for the human albumin gene. However, while these promoters exhibit tissue specificity, they also exhibit a relatively low strength. ***Thus, the great majority of these promoters possess levels of activity that are well below the activity of so-called "strong" promoters, generally by a factor of between at least 10 and 100.*** In addition, it is generally considered that the specificity of a promoter is inversely proportional to its strength, and that the higher the strength of the promoter, the higher the level of nonspecific activity.

(*Id* (emphasis added)).

It is respectfully submitted that this passage makes clear that a "strong" promoter is a promoter, which is very active so that the gene that is operatively associated with a strong promoter is easily expressed, yet is not very specific with respect to the cell in which the promoter function. Hence, as Applicants state, the strength of a promoter is inversely proportional to its specificity. Indeed, it is this very problem the instant Invention is intended to overcome. MPEP 2111.03 clearly explains that an applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the

term's well known usage.(See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). Moreover, in *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999), the Court of Appeals for the Federal Circuit specifically stated:

> In judicial "claim construction" the court must achieve the same understanding of the patent, as a document whose meaning and scope have legal consequences, as would a person experienced in the technology of the invention. Such a person would not rely solely on a dictionary of general linguistic usage, but would understand the claims in ***light of the specification and the prior art***, guided by the prosecution and experience in the technologic field.

(53 USPQ2d at 1068 (emphasis added)).

In light of the instant Disclosure, the term "strong" as used in the pending Claims is readily definite to one of ordinary skill in the art, and this rejection should be withdrawn.

Furthermore, the Examiner has also asserted that Claim 2 is indefinite in that it claims a hybrid promoter chosen from CMV-IE, RSV-LTR, the SV40 enhancer and the EF1a enhancer. It is the Examiner's belief that it is not clear whether the promoter is all four, or only one element chosen from the list. Similarly, the Examiner has asserted that Claim 10 is indefinite in that it claims a protein chosen from the proteins involved in cell cycle etc. and transcription factors.

In response, it is noted that Claim 2 has be amended to be directed towards, *inter alia*, a hybrid promoter wherein the enhancer region is selected from the group consisting of: the enhancer region of the cytomegalovirus immediate- early (CMV-IE) gene; the enhancer region of the rous sarcoma virus L TR (RSV-L TR); the enhancer region of the SV40 virus; and the enhancer region of the EF1a gene. Likewise, Claim 10 has been amended to be directed towards, *inter alia*, an expression cassette in which the nucleic acid encodes a protein selected

from the group consisting of a protein involved in the cell cycle, a protein that induces apoptosis, a protein capable of modifying the proliferation of smooth muscle cells, a protein that induces angiogenesis, and a transcription factor. It is respectfully submitted that amended Claims 2 and 10 are readily definite, and this rejection should be withdrawn.

The Examiner has also asserted that Claims 17 and 18, which provide for the use of hybrid promoters are indefinite because they do not set forth any steps involved in the method/process, and the Examiner believes it is unclear what method/process applicant is intending to encompass. The Examiner has further rejected Claims 17 and 18 under 35 U.S.C. § 101 because, in the Examiner's opinion, the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process. In response, it is respectfully pointed out to the Examiner that Claims 17-18 have been canceled, without prejudice. Hence, this rejection is moot.

In light of the above, amended Claims 1-15, as well as new Claims 19-20 are clearly definite to one of ordinary skill in the art, and these rejections should be withdrawn.

Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

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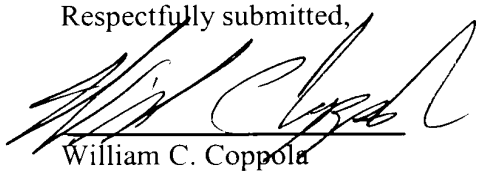
CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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Version With Markings To Show Changes Made

Material that has been added is underlined, and material that has been removed is within brackets.

IN THE SPECIFICATION:

A substitute specification and formal drawings are filed herewith.

IN THE CLAIMS:

1. (Amended) A hybrid [Hybrid] promoter comprising:

(a) an [-all or part of the] enhancer region of a strong and ubiquitous promoter/enhancer, and

(b) a [-a] promoter region that allows [allowing] specific expression in [the] smooth muscle cells,

wherein said enhancer region and said promoter region are less than 1 kb apart.

2. (Amended) The hybrid [Hybrid] promoter according to claim 1, wherein [characterized in that] the enhancer region is selected from the group consisting of: [chosen from] the enhancer region of the cytomegalovirus immediate- early (CMV-IE) gene[,] ; the enhancer region of the rous sarcoma virus L TR (RSV-L TR)[,]; the enhancer region of the SV40 virus[,]; and the enhancer region of the EF1a gene.

3. (Amended) The hybrid [Hybrid] promoter according to claim 2, wherein [characterized in that] [the enhancer region is] the enhancer region of the cytomegalovirus immediate-early [gene of the cytomegalovirus] (CMV-IE) gene is [, preferably of] the human cytomegalovirus (hCMV-IE).

4. (Amended) The hybrid [Hybrid] promoter according to claim 1, wherein [characterized in that] the promoter region comprises [all or part of] the promoter of the gene encoding [the a-actin] α-actin of smooth muscle cells (SMact), or the promoter of [or of] the SM22 gene.

5. (Amended) A hybrid [Hybrid] promoter comprising:

(a) an [-all or part of the] enhancer region of the human cytomegalovirus immediate-early (hCMV-IE) gene, and

(b) a promoter [-all or part of the promoter] of the gene encoding the α-actin [a-actin] of smooth muscle cells (SMact),

wherein said enhancer region and said promoter are less than 1 kb apart.

6. (Amended) A hybrid [Hybrid] promoter comprising:

(a) an [-all or part of the] enhancer region of the human cytomegalovirus immediate-early (hCMV-IE) gene, and

(b) a [-all or part of the] promoter of the SM22 gene,

wherein said enhancer region and said promoter are less than 1 kb apart.

7. (Amended) The hybrid [Hybrid] promoter according to claim 1, wherein [characterized in that] the promoter region comprises a basal promoter and a sequence conferring tissue specificity that is derived [, said sequence being derived] from the SMact promoter, the SM22 promoter, or from

a combination of the SMact promoter and the SM22 promoter [and/or from the SM22 promoter].

8. (Amended) An expression [Expression] cassette comprising a nucleic acid that is complementary to [encoding] an RNA or encodes a polypeptide of interest, that is placed under the control of a hybrid promoter of Claim 1 [according to one of claims 1 to 7].

9. (Amended) The expression cassette [Cassette] according to claim 8, further comprising [characterized in that it comprises in addition,] a signal for termination of transcription.

10. (Amended) The expression cassette [Cassette] according to claim 8 [or 9], wherein [characterized in that] the nucleic acid encodes a protein selected from the group consisting of [chosen from the proteins] a protein involved in the cell cycle, a protein that induces [the proteins inducing] apoptosis, a protein [the proteins] capable of modifying the proliferation of [the] smooth muscle cells, a protein [the proteins inducing] that induces angiogenesis, and a [the] transcription factor [factors].

11. (Amended) A vector that comprises: [Vector comprising a hybrid promoter according to claim 1]

(a) a hybrid promoter comprising:

(i) an enhancer region of a strong and ubiquitous promoter/enhancer, and

(ii) a promoter region that allows specific expression in smooth muscle cells,

wherein said enhancer region and said promoter region are less than 1 kb apart; or

(b) a cassette according to claim 8.

12. (Amended) The vector [Vector] according to claim 11, wherein said vector is [characterized in that it is] a plasmid, a cosmid or any DNA not encapsidated by a virus.

13. (Amended) The vector [Vector] according to claim 11, wherein said vector [characterized in that it] is a recombinant virus[, preferably derived from an adenovirus, a retrovirus, a herpesvirus or an adeno-associated virus].

14. (Amended) A composition [Composition] comprising the [a] vector according to claim 12 and a chemical or biochemical transfer agent.

15. (Amended) A composition [Composition] comprising the vector [a recombinant virus] according to claim 13 and a physiologically acceptable vehicle.

16. (Amended) A cell [Cell] modified by:

(a) a cassette according to claim 8; or

(b) a vector that comprises a hybrid promoter comprising an enhancer region of a strong and ubiquitous promoter/enhancer, and a promoter region that allows specific expression in smooth muscle cells, wherein said enhancer region and said promoter region are less than 1 kb apart

[according to claim 11].